Diffraction from single particles and much, much more...

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"... lack of information cannot be remedied by mathematical trickery."

Cornelius Lánczos.

Three talks for the price of one.

1.) Methods to get the (continuous) diffraction pattern of a single particle from an ordered array – a crystal.

2.) The intimate connections among "diffraction", "holography" and "crystallography". (Rated R.)

3.) Our recovery program, EDEN, that is different from the iterative algorithms.

Method # 3:

Low energy electron diffraction from a partial overlayer on a crystal surface. (D. Saldin, K. Heinz.)

Usually, an adsorbed atom or molecule sits in a well defined position on the surface of the crystal, *i.e.* all of them have the same close environment.

When the number of adsorbates is small (compared to the number of unit cells on the surface), they sit in unit cells at random.

When the crystal surface diffracts low energy electrons, we get a diffuse diffraction pattern, even though the incident electrons are coherent over many unit cells. (DLEED)

The diffraction pattern is that of a single adsorbate and its close environment. Its intensity is the sum of the individual diffraction patterns. The interference term among different adsorbates averages out.

Method # 2:

# Diffraction of a crystal with two kinds of molecules.

We assume that the two kinds of molecules are similar and that they are
   thoroughly mixed.

We can define an average density of the two molecules, and a difference
   density.

- The average density is periodic: it gives Bragg peaks.
- The difference density produces a continuous diffraction pattern of
   the difference molecule.

We simulated time resolved chemistry in crystals:

A reaction is initiated in a fraction of the molecules (e.g. by a short
   pulse laser.) A monochromatic X-ray pulse irradiates the crystal
   with a time delay. The diffraction pattern is recorded.
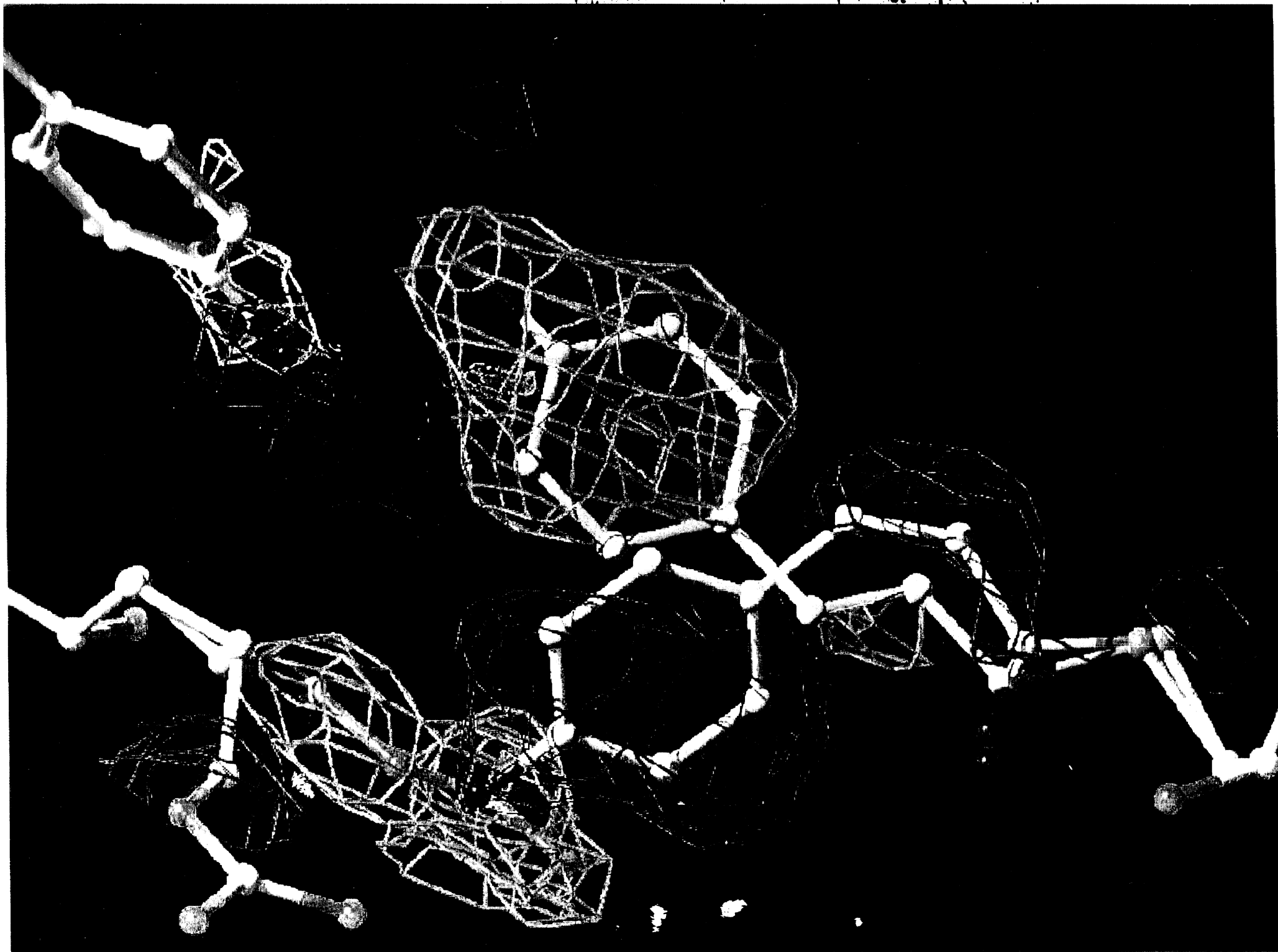
Method # 1:

Diffraction of X-rays with limited coherence from crystals.

Assume that the incident X-rays are concentrated on a single molecule in the crystal. Obviously, we get the (continuous) diffraction pattern of that single molecule.

Now irradiate another molecule in the crystal with an independent X-ray source. In the far field, it produces the <u>same</u> diffraction pattern.

The <u>intensity</u> of the diffraction pattern of the two molecules is the sum of the intensities of the individual diffraction patterns.

By limiting the coherence length of the incident X-rays, individual molecules in the crystal are irradiated by statistically independent X-ray beams. The result is the sum of the intensities of the (continuous) diffraction patterns of all molecules.

Detailed calculations will appear in Acta Cryst. A.

There is a method to my madness...

In biology, resolution is limited by **damage**.

For <u>long pulses</u>, in frozen samples, the damage limit is $2 - 5$ eV/atom, or $50 - 125$ kCal/mole.

For 300 keV electrons,
    the limit is 5 electrons/$\mathring{A}^2$

For 10 keV photons and large objects,
    the limit is 200 photons/$\mathring{A}^2$

For 10 keV photons and small objects,
    the limit is 4000 photons/$\mathring{A}^2$

All pulses longer than a few femtoseconds are long.

The simplest way around damage is to have many specimens that give the same hologram.

The intimate connections among diffraction, tomography and holography.

Let us assume that we have one small particle.

Let us illuminate the small particle with a parallel beam (a far away source).

If the detector is also far away, we get a (regular) diffraction pattern.

If part of the particle is known, we get a hologram with a complicated reference.

If the detector is close, we get a tomogram. If the detector is not so close, we get a diffraction tomogram.

Finally, let us bring the source close. Then we get a hologram with a local reference.

Holographic Microscopy with a Local Reference

Detector

Reference

Object (scatterer)
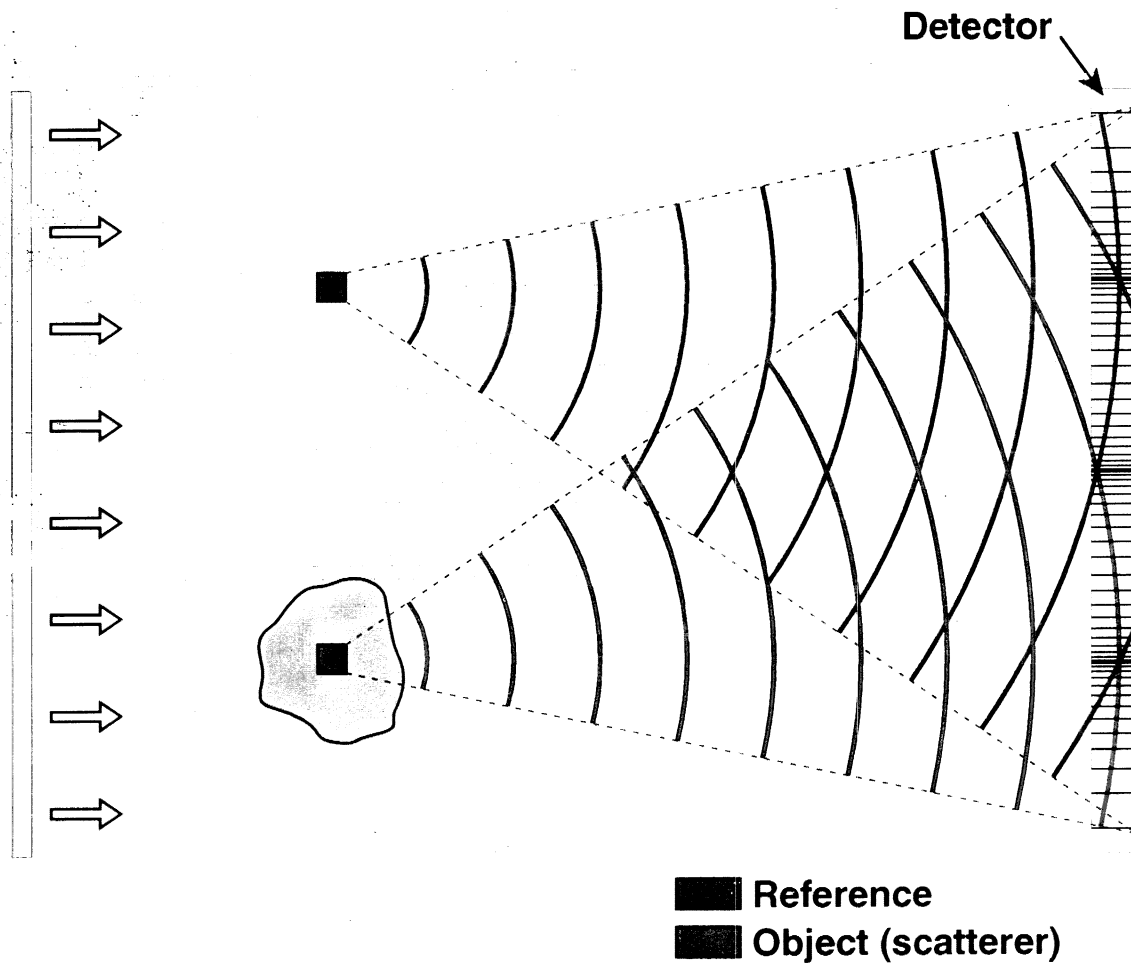
Holography with a local reference.

Local reference means that the reference point is at a few wavelengths away from the object.

Large fringes

Low coherence requirement

Stability

"Real" holograms:

Electron microscopists have produced holograms with high resolution.

Holograms produced by electrons emitted from a needle with a single atom tip come close to it.
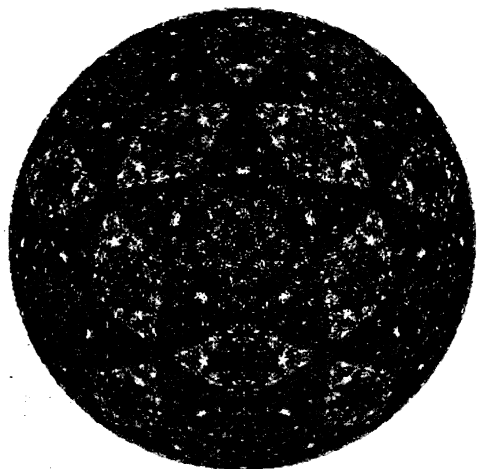
"Funny" holograms:

Photoelectron holography
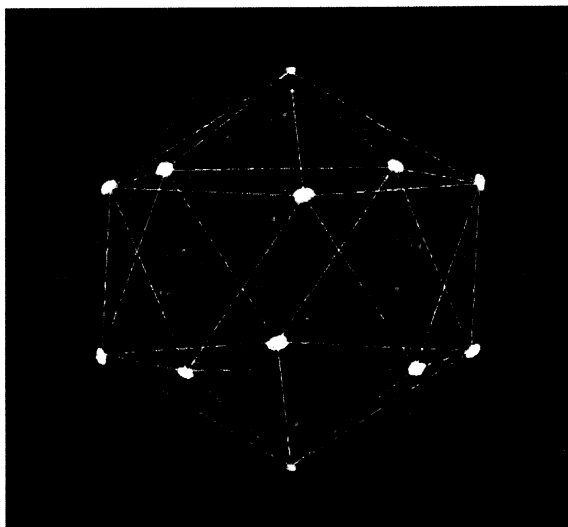
X-ray emission holography

Inverse X-ray holography

"Funny" holograms have many incoherent sources with similar surroundings. The intensities of the individual holograms add up to a single hologram. The hologram measures only local order.

$Al_{70.4} Pd_{21} Mn_{8.6}$ Quasicrystal

Hologram

(16 keV, inverse mode.
T. Gog *et al.,* Phys. Rev.
Lett. 76, 3132 (1996).)

Reconstruction,

J. J. Barton, Phys. Rev. Lett.
67, 3106 (1991).

S. Marchesini, et al. Phys. Rev. Lett. **85**, 4723 (2000)

Holography with a Complicated Reference

It is a small further step to extend holography to a complicated reference.

Suppose, we know the structure of a part of a molecule (also, where it is.) Let us irradiate the whole molecule with X-rays. We can regard the diffraction pattern as a hologram with a complicated reference.

■ Known part
▨ Unknown part
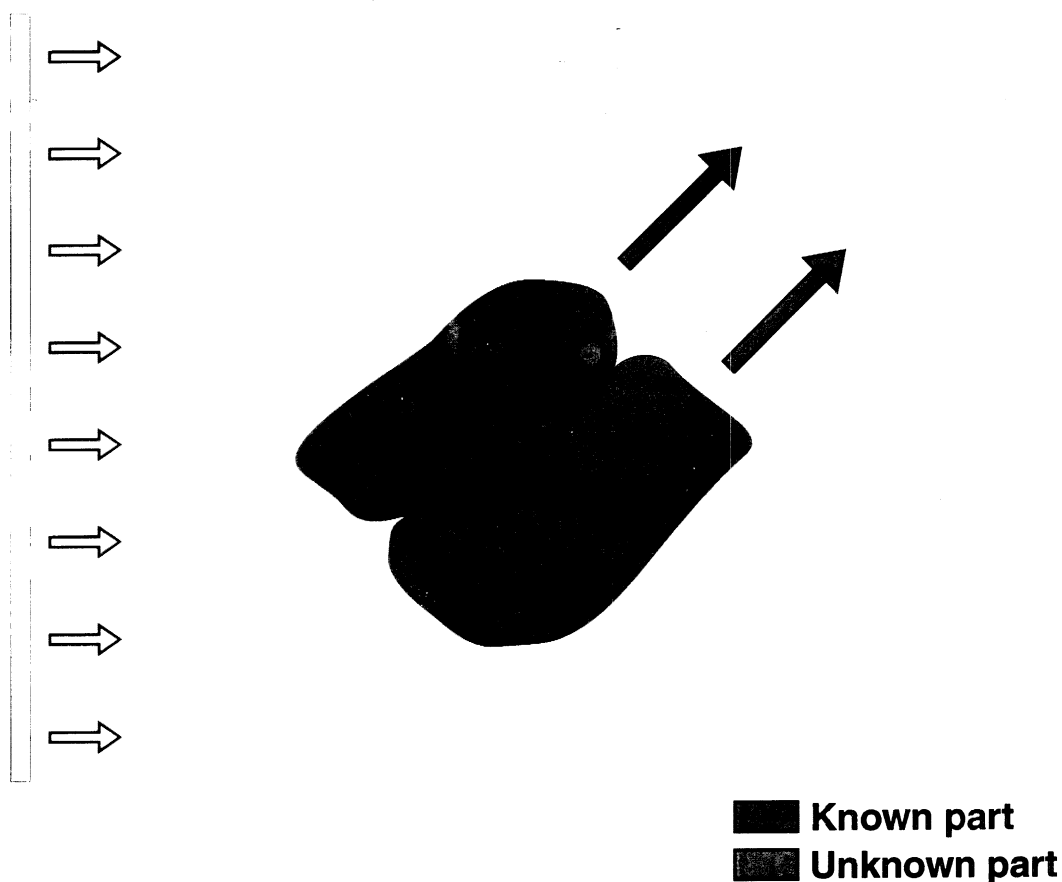
Holography with a local, <u>complicated</u> reference.

"Real" holograms:

Diffraction from a particle that is partly known.

"Funny" holograms:

Partial overlayers on crystals

Mixed crystals

Partly coherent X-rays

These have many <u>effectively</u> incoherent sources with similar surroundings. The intensities of the individual holograms add up to single hologram. Only local order is important.

"Even funnier" holograms:

X-ray crystallography

The diffraction patterns of each unit cell add up coherently. The result is the diffraction pattern of a single unit cell that is sampled in directions that satisfy the Bragg condition.

Recovery of the scatterer, or the "holographic" inverse problem.

Methods with "perfect" recovery:

Inverse X-ray holography

Photoelectron holography

Partial molecular overlayers

Near field methods, e.g. tomography

Methods with a dual image problem (but not really bad):

X-ray emission holograms

Diffraction from a single particle

Mixed crystals

Partly coherent X-rays

Methods with a phase problem (BAD):

Conventional X-ray crystallography

EDEN, a holographic method for X-ray crystallography.

Abraham Szöke, Hanna Szöke

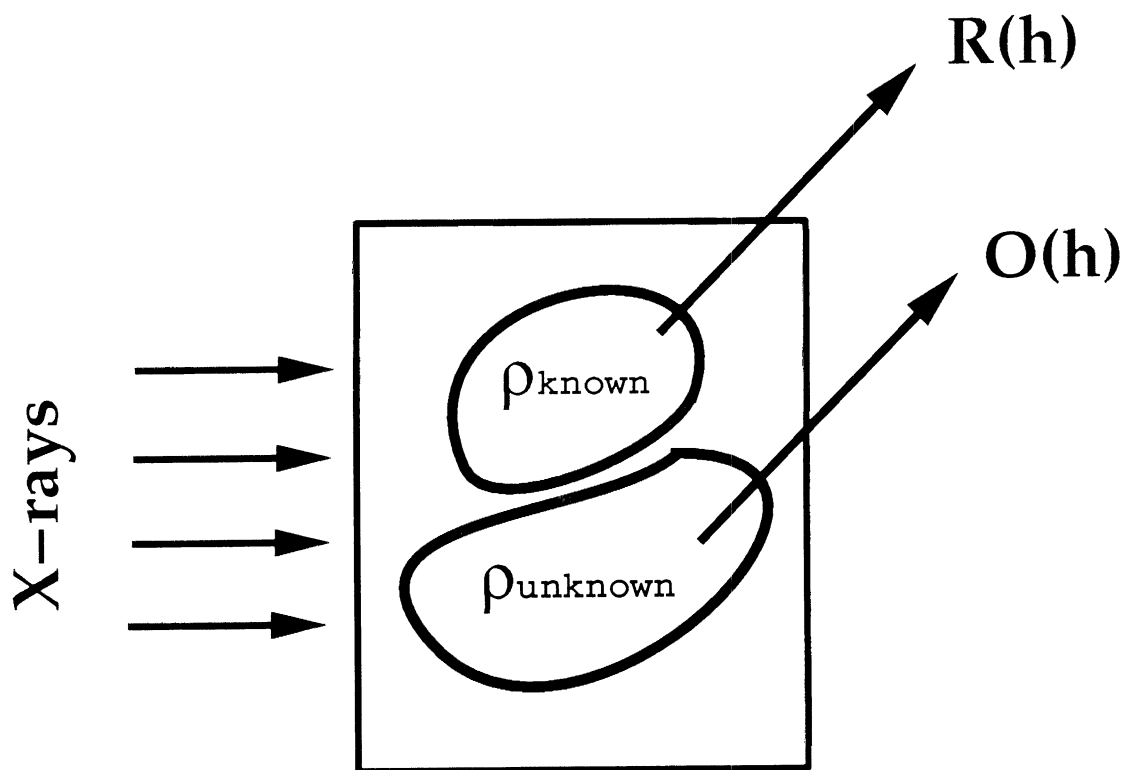Lawrence Livermore National Laboratory

Livermore, CA 94551

and

John R. Somoza

Axys Pharmaceuticals, San Francisco.

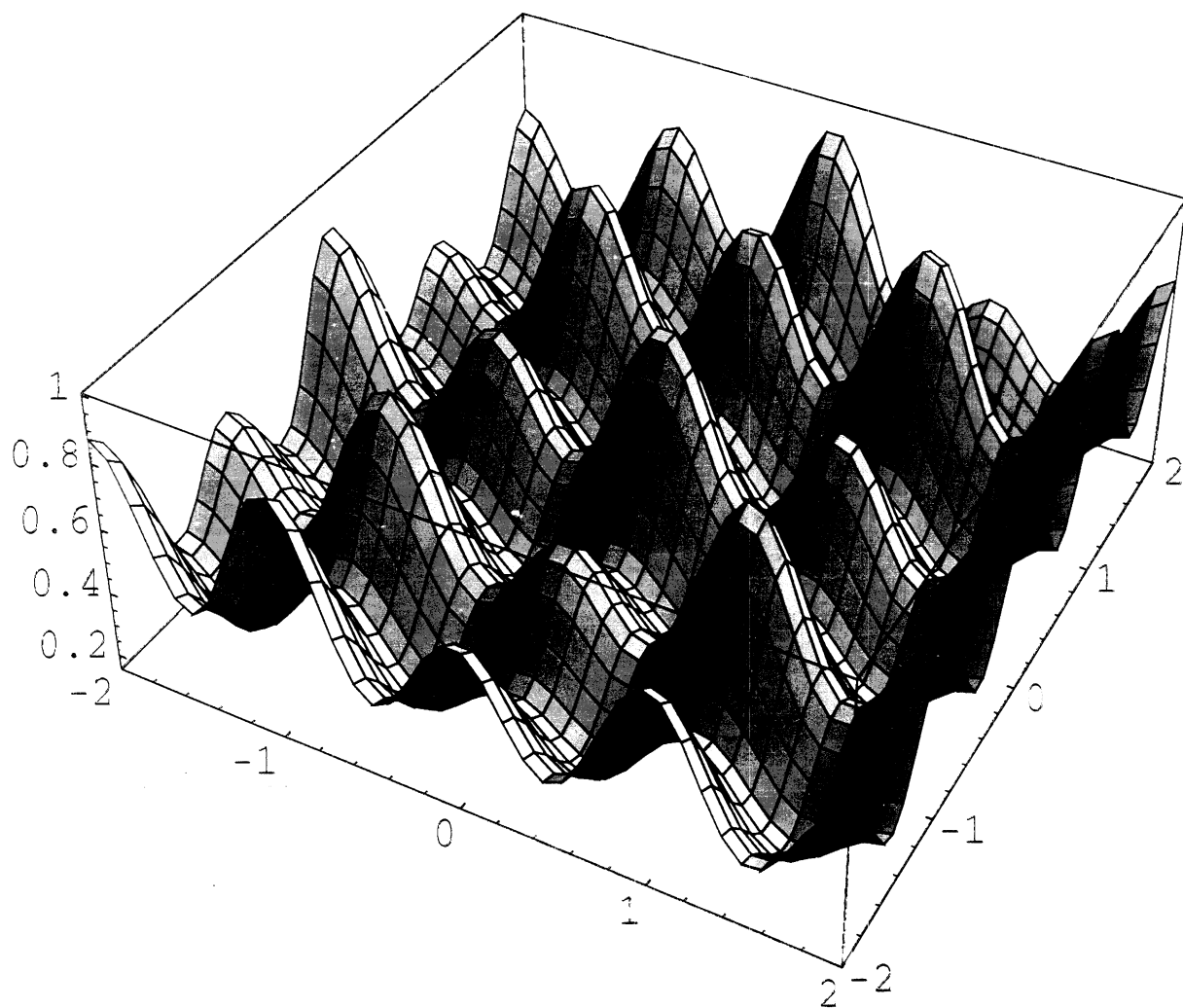We view crystallography as holography with a complicated reference.

As this is the most difficult one of those problems, the program solves the easier problems too.

$$\rho_{\text{total}}(r) = \rho_{\text{known}}(r) + \rho_{\text{unknown}}(r)$$

$$F(h) = R(h) + O(h)$$

Representing the Electron Density
in Terms of Gaussian Basis Functions

Representing Electron Density in Terms of Gaussians on a Grid

One Gaussian:

$$n(p) \frac{1}{(\pi d^2)^{3/2}} \exp\left[\frac{-|\mathbf{r}-\mathbf{r}(p)|^2}{d^2} \right]$$

Total electron density:

$$\rho(\mathbf{r}) \approx \frac{1}{(\pi d^2)^{3/2}} \sum_{p=1}^{P} n(p) \exp\left[\frac{-|\mathbf{r}-\mathbf{r}(p)|^2}{d^2} \right]$$

Theory

$$\rho total(\mathbf{r}) = \rho known(\mathbf{r}) + \rho unknown(\mathbf{r})$$

$$F(\mathbf{h}) = \int_{unit\ cell} \rho total(\mathbf{r}) \exp(2\pi i \mathbf{h} \cdot \mathcal{F}\mathbf{r})\ d\mathbf{r}$$

$$R(\mathbf{h}) = \int_{unit\ cell} \rho known(\mathbf{r}) \exp(2\pi i \mathbf{h} \cdot \mathcal{F}\mathbf{r})\ d\mathbf{r}$$

$$O(\mathbf{h}) = \int_{unit\ cell} \rho unknown(\mathbf{r}) \exp(2\pi i \mathbf{h} \cdot \mathcal{F}\mathbf{r})\ d\mathbf{r}$$

$$|F(\mathbf{h})|^2 = |R(\mathbf{h}) + O(\mathbf{h})|^2$$

$$= |R(\mathbf{h})|^2 + R(\mathbf{h})\ O^*(\mathbf{h}) + R^*(\mathbf{h})\ O(\mathbf{h}) + |O(\mathbf{h})|^2$$

Theory (continued)

$$\rho_{unknown}(\mathbf{r}) \approx \frac{1}{(\pi\eta\Delta r^2)^{3/2}} \sum_{p=1}^{P} n(p) \; \exp\left[\frac{-|\mathbf{r}-\mathbf{r}_p|^2}{\eta\Delta r^2}\right]$$

$$O(\mathbf{h}) = \sum_{p=1}^{P} n(p) \; O_p(\mathbf{h}) = \exp\left[-\eta(\pi\Delta rd)^2\right] \sum_{p=1}^{P} n(p) \; \exp(2\pi i\mathbf{h}\cdot\mathbf{x}_p)$$

$$|F(\mathbf{h})|^2 = |R(\mathbf{h}) + O(\mathbf{h})|^2 =$$

$$|R(\mathbf{h})|^2 + \sum_{p=1}^{P} n(p) \; [O_p^*(\mathbf{h})R(\mathbf{h}) + O_p(\mathbf{h})R^*(\mathbf{h})] + |\sum_{p=1}^{P} n(p) \; O_p(\mathbf{h})|^2$$

Theory (finally...)

In order to find the missing electrons, we minimize the squared difference between the two sides of the last equation:

$$\text{feden} = \frac{1}{2} \sum_{h} w(h)^2 \ [\,|\,R(h) + O(h)\,| - |\,F(h)\,|\,]^2$$

In the final analysis, the method is a real space method.

It uses a basis function expansion of the electron density.

(It has all sorts of mathematical, and computational subtleties:

Gabor wavelet expansion, most stable recovery, $1/\sigma^2$ weights, fast Fourier transforms, all Fourier transforms in the stable directions, the ease to add restraints.)

Real space cost function.

The target density is described by a set of "densities" {$n(p)_{target}$} and a weight array w_p^2.

The weight array can be positive in only part of the unit cell.
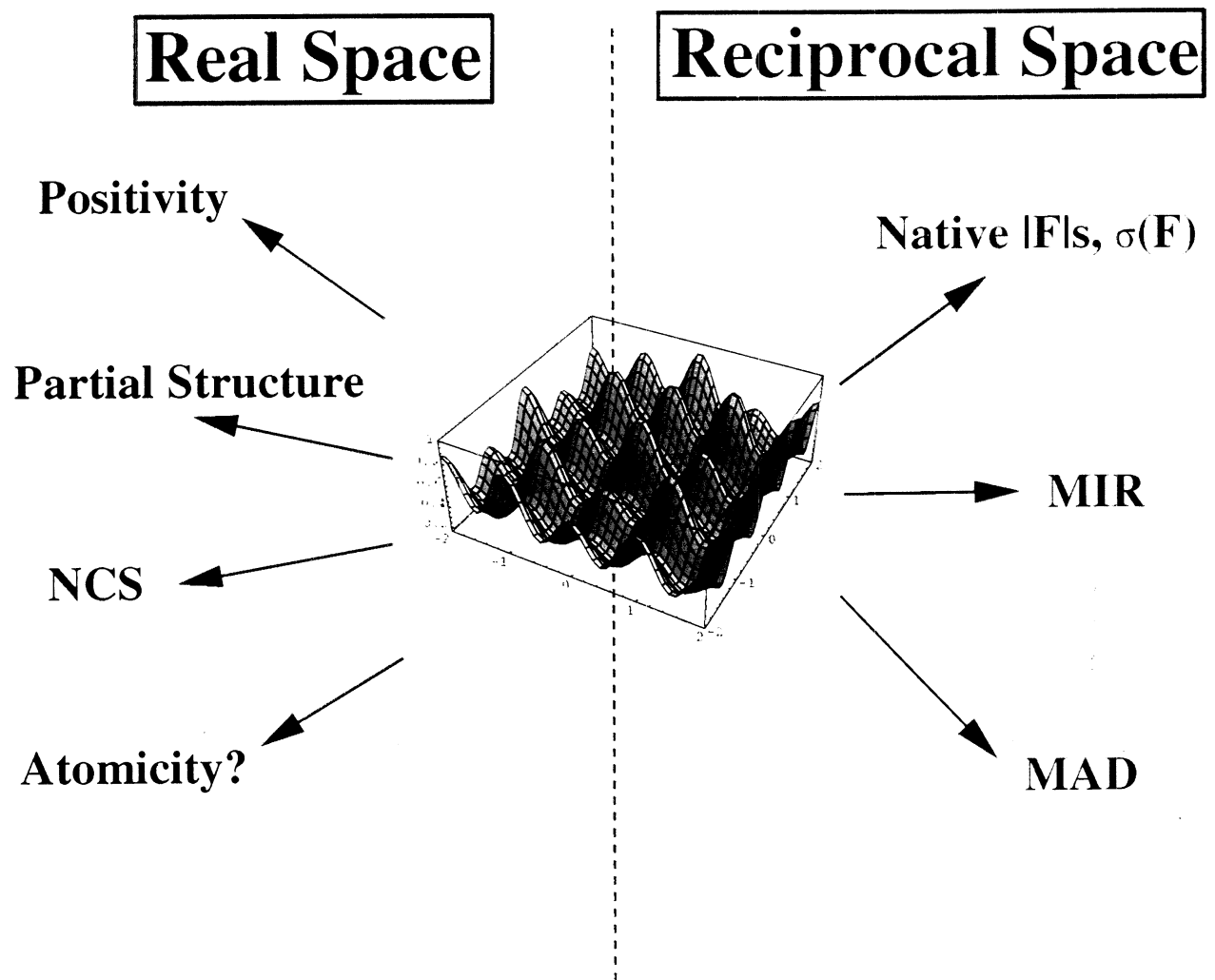
The cost function to be minimized is

$$f_{space} = \frac{1}{2} \lambda_{space} P \sum_{p=1}^{P} w_p^2 \, (n(p) - n(p)_{target})^2$$

λ_{space} gives the relative importance of the spatial knowledge to that of the structure factors.

The total cost function is the sum of its ingredients

$$f_{total} = f_{eden} + f_{space}$$

Restraining the Electron Density

| Real Space | Reciprocal Space |

Positivity

Partial Structure

NCS

Atomicity?

Native |F|s, $\sigma(F)$

MIR

MAD

Forward and inverse problems.

Forward problems:

$$F(\mathbf{h}) = \int_{unitcell} \rho(\mathbf{r}) \exp[2\pi i \mathbf{h} \bullet \mathbf{r}] d\mathbf{r}.$$

It is "easy" to calculate the structure factors from a known electron density. Small errors in electron density cause small errors in the structure factors.

Inverse problems:

$$\rho(\mathbf{r}) = \sum_{\mathbf{h}} F(\mathbf{h}) \exp[-2\pi i \mathbf{h} \bullet \mathbf{r}].$$

It is "hard" to calculate the electron density from the structure factors. Small errors in structure factors cause large errors in electron density. This is called "ill-conditioning".

It is also known (Sayre, 1952) that the number of measurable structure factors is sparse enough that that all structure factor amplitudes and phases are needed to find a unique electron density.

(In information theory jargon this is called critical sampling.)

This brings us to the infamous crystallographic phase problem …

The crystallographic phase problem.

The phase problem:

$$F(\mathbf{h}) = |F(\mathbf{h})| \exp[i\phi(\mathbf{h})].$$

We can only measure the amplitudes of the structure factors. Therefore, information is missing.

The inevitable consequence is that there are many different electron densities that produce the same measured diffraction amplitudes.

Conclusion: in the crystallographic inverse problem one has to deal with ill-conditioning and one needs additional information.

Some details of our X-ray crystallography program.
(For cognoscenti of inverse problems...)

The inverse problem is unstable for two reasons:
    There is a large null space - this is the "phase problem".
    Even within the non-null space the forward matrix is ill
   conditioned.

The "phase problem" can only be solved by additional information.

The ill conditioned part has to be stabilized. Ill conditioning comes
    from the high resolution (measured) structure factors.
For stabilization we apodize the observed structure factor amplitudes.
    (They are multiplied by a Gaussian that fits the resolution of the
    basis set.)
No other stabilization is used.

**Dennis Goodman's conjugate gradient algorithm is used to
solve the quadratic programming problem.**

X-RAY DATA COLLECTION

a   b   c   d   e

Berglund et al. Figure 3
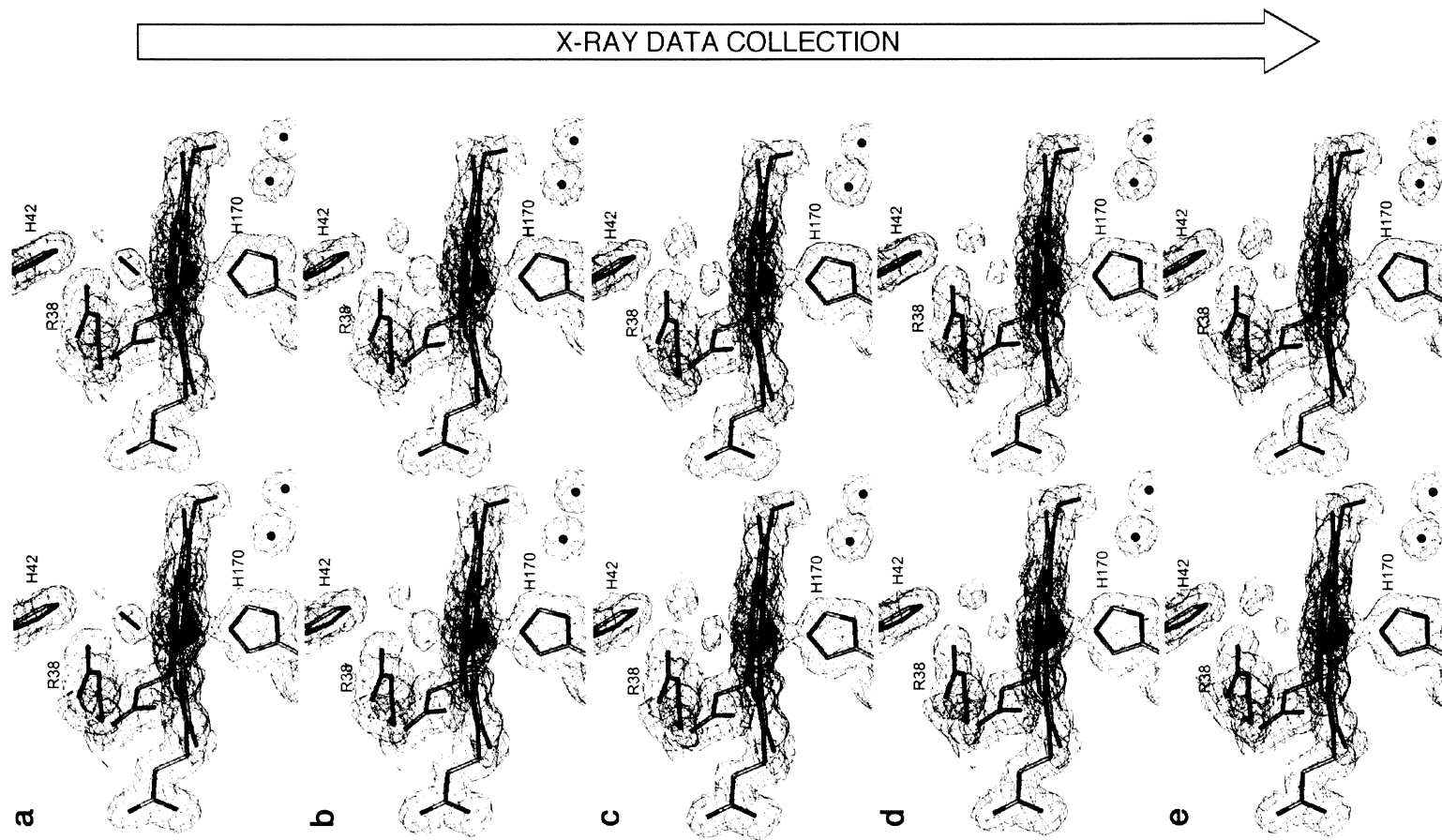
Summary.

There is a close relation between X-ray crystallography and
holography. (Gabor credited Bragg with sparking his ideas.)
A continuous diffraction pattern of a molecule can be sampled finely
enough to reconstruct it. (Except for minor details.)
I have shown several ways to produce a continuous diffraction pattern
of a single molecule when only a crystal is available:
a local reference (inverse) hologram,
a partial overlayer,
a short coherence X-ray beam and
a crystal lattice randomly occupied by two different molecules.
All of these methods are designed to overcome damage by adding
together the diffraction intensities of all similar molecules.
Our crystallographic program, EDEN, is a real space, wavelet based
optimizer. It stabilizes the inverse problem, it incorporates
experimental errors as well as other information consistently.
It gives model free electron densities.
Naturally, the program can handle the much easier problems of single
particle diffraction and tomography.

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